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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/124,485	07/29/1998	NICHOLAS MARK ANSTEY	73-97	6763

23713 7590 01/18/2006

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/124,485	ANSTEY ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33,38,40,41,46 and 48* is/are pending in the application.

4a) Of the above claim(s) *27-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, 40-41, 46, 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's response filed on 11/1/2005 has been received and entered into record and considered.

1. Claim 1-26, 34-37, 39, 42-45, 47 are cancelled. Claims 27-33 are withdrawn.
2. Currently, claims 38, 40-41, 46, 48 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of enablement

In vivo application

2. Claims 38, 40-41, 46, 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro, does not reasonably provide enablement for in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to apply the invention commensurate in scope with these claims.

As set forth in *In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The current case recites a method for the treatment of infection by a *Plasmodium* species in human, by administering an agent capable of increasing the level of nitric oxide in the body. The *Plasmodium* infected disease is particularly on malaria. Although applicant discloses general protocols in selecting patients, dietary control, sample collection, nitrate administering and measuring NO level, statistically analysis method, readjusting confounding factors, such as renal failure. (See examples 1-21) The results in this instant application do not provide sufficient information or guidance to one ordinary skilled in the art to use or conduct the recited method in achieving the claimed effect, particularly in vivo.

Applicant provides data with respect to the inhibition of cytoaherence of infected RBC to C32 melanoma cells. (See Figure 1 and 2) The inhibition of cytoadherence has been shown "reduces the *likelihood* of infection of severe infection by Plasmodium species." (See page 14, last paragraph) Those data represent in vitro correlation between the different Plasodium strains (Figure 1) and the level of S-nitrosylation on RBC (Figure 2). Applicant asserts that the data support the notion that *RSNO treatment of parasitised red blood cells* inhibits cytoadherence to *C32 cells*. (See page 34, line 27-28) (emphasis added) This example merely shows an in vitro treatment on parasitised red blood cells, not an in vivo treatment on host, such as human. There is no causal-effect relationship, i.e. decrease the severity of malaria disease. The data merely provides observation of the treatment on parasitised red blood cells with the RSNO.

The issue is that whether this in vitro model is an adequate model to reflect the effectiveness of an in vivo treatment on human. In another word, whether the disclosed information in this application would enable one ordinary skill in the art to conduct the recited method without undue experimentation for the effectiveness in vivo.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area, the more specific enablement is necessary in order to satisfy the statutory requirement of 35 U.S.C §112, first paragraph. Applicant submits several review articles concerning the cytoadherence in vitro analysis (Note, ***after*** priority date; See below). In view of the current evidence, the instant

cytoadherene in vitro assay does not support the notion of adequate *extrapolation* to the in vivo extrapolation (emphasis added).

The instant claimed method relies on administering agents having effect on nitric oxide (note, not claimed but deleted during prosecution) to host parasitized by Plasmodium mosquito. The agents include L-arginine, NO gas and /or S-nitrosothiol.

With respect to administering of arginine to the human subjects, applicant submitted his own post-filing date publication and argues that the claimed methods are applicable to the treatment of malaria disease (See page 7, first paragraph; See Exhibit I, *Anstey et al. Am. J. of Tropical Medicine and Hygiene (2002) 67(2): abst. 515*). In review of this publication, *no data or results have been shown to the treatment of malaria by administering agents* to increase nitric oxide levels (emphasis added).

The conclusion of this publication is that there exists an inverse relationship between Plasmodium malaria patients and the level of nitric oxide in the patients. Furthermore, another applicant's own post-filing date reference also *no record of administering L-arginine to patients*, concerns uncertainty with respect to the treatment or prevention of the current purported method (See Exhibit A, The *LANCBT 2003 Vol. 361: 676*)(emphasis added). Applicant states that "[w]hether or not severe disease is caused by, or results from, hypoargininsemia is *unclear*" (See page 677, right column, fourth paragraph)(emphasis added). Additionally, applicant concludes that "[c]linical trials are warranted to *ascertain* whether or not correction of L-arginine deficiency provides adjunctive prophylactic and therapeutic benefit to malaria" (See page 678, left column, last paragraph)(emphasis added). In another word, nearly 5- year after filing this application (filing date 7/9/1998), there is still some uncertainty concerning the in vivo effects, i.e. prevention and treatment.

The specification does not teach how to extrapolate data obtained from in vitro assays to the development of effective in vivo human treatment, commensurate in scope with the claimed invention. In view of the aforementioned lack of predictability in the art, undue experimentation

would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the applicant's specification of how to effectively practice the recited method and absent working examples.

Written Description

3. Claims 38, 40-41, 46, 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the instant invention, particularly the in vitro data of cytoadherence, is an adequate extrapolation of the in vivo situation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483.

In view of the specification, the present application merely shows data of in vitro treatment of agents effecting cytoadherence of parasited RBC on nitric oxide. Although applicant disclose some clinical aspects for the in vivo treatments and analysis, e.g. example 1-12; 16-23, nevertheless the protocols can only be considered as a preparation for the future study to ascertain the in vivo effects based on the existing in vitro data. At most, it would motivate one

ordinary skill in the art to conduct further research. But one artisan in the art would not have concluded that applicant possesses the recited method in commensurate with the scope of its claimed invention, particularly with aspect of in vivo due to the uncertainty and unpredictability of the art at the *filing date* of this application (emphasis added; See above discussion on the post-filing date of applicant's own publication). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 38, 40, 46, 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Rockett et al. (Infection Immunity 1991, Vol. 59, page 3280).

Rockett et al. teach a method of killing Plasmodium falciparum in vitro by nitric oxide derivatives (S-nitrosothiol), such as S-nitrosoglutathione or S-nitrocysteine (See Abstract and Table 2). The killing of Plasmodium would reduce or inhibit of its attach on the target red blood cells, thus diminish the pathological adherence of the parasitized red blood cells (See page 3281, right column, third paragraph). The inhibiting concentration on Plasmodium in vitro is 39.10 uM and 41.86 uM for S-nitrosoglutathione and S-nitrocysteine, respectively (See Table 2).

6. Claims 38, 40, 46, 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Stamler et al. (US 6153186).

Stamler et al. teach a method of treating the infected Plasmodium falciparum patient ex vivo by using the nitrothiol compounds, such as S-nitrocysteine, or S-nitroglutathione (See Col. 6, line 5-20; 26-39).

Response to Applicant's Arguments

Scope of Enablement/Written Description

7. Applicant's arguments on the cytoadhereence model has been considered persuasive, but examiner maintains scope enablement rejection in view of applicant's own publications Anstey et al. (Am Trop Med Hyg 2002 Vol. 67, page 515) and Lopansri et al. (LANCBT 2003 Vol. 36, page 676)(See above discussion).

Applicant argues that the concerns for uncertainty for treatment using L-arginine is "[s]uch conservative expressions are standard in all medical journals and are often required by journal editors until therapeutic role is proven beyond any doubt in at least one large randomized clinical trial" (See Remarks on page 5, second paragraph). Applicant also submits several articles showing that the relationships of administering L-arginine to patients and the production of nitric oxide.

Applicant's arguments have been considered but are not persuasive.

First of all, the post-filing date publications of applicant support examiner's position with respect to the scope of enablement as discussed above. Additionally, the "conservative expression standard in the medical journals" further strengthens the uncertainty of the in vivo treatment and the effectiveness. Particularly, examiner would like to reiterate that

no in vivo data, i.e. administering to Plasmodium infected patients with L-arginine, from these two publications (nearly 5 years later post filing date) have ever presented (emphasis added). Particularly, applicant's publications merely show an inverse relationship between the infected patients and the level of nitric oxide. It may require a leap of faith to jump to a conclusion that by administering nitric oxide inducer, such as L-arginine would remedy the problem.

Examiner acknowledges the feasibility of administering L-arginine in vivo with *other effects*, such as in platelet aggregation, vasodilation and thromboxane synthesis (emphasis added)(See references from Exhibits A-E submitted 11/1/2005). None of the references disclose or imply the relationship of L-arginine with the infection of Plasmodium. The issue is whether one ordinary skill, in view of the current specification and the in vitro data, can conclude that applicant possesses the invention for in vivo treatment, and would not be required to practice/or use the recited method without undue experimentation. Examiner does not find the instant application providing sufficient information to warrant possession and enablement.

8. The rejection of 35 USC 102 (b) as anticipated by Rockett et al. is maintained.

Applicant argues that Rockett et al. does not teach or suggest a protective role for NO in malaria since prior to application, most researchers emphasizing pathogenic role of NO, not protective role of NO.

Applicant's argument has been considered but is not persuasive.

Regardless of opinions of other scientists in the field, the recited claim speaks for itself.

The current claim recites administering an agent, i.e. L-arginine, NO gas and/or S-nitrosothiol compound to a host parasitized by Plasmodium for inhibiting, retarding or killing of cycle stages of Plasmodium (See claim 38).

The reference of Rockett et al. title is "*Killing of Plasmodium falciparum In vitro* by Nitric Oxide derivatives" (emphasis added). Rockett et al. reference teaches using S-nitrosoglutathione or S-nitrocysteine (See Abstract and Table 2) for killing of Plasmodium which would reduce or inhibit of cytoattachment on the target red blood cells, thus diminish the pathological adherence of the parasitized red blood cells (See page 3281, right column, third paragraph). The inhibiting concentration on Plasmodium in vitro is 39.10 uM and 41.86 uM for S-nitrosoglutathione and S-nitrocysteine, respectively (See Table 2). The data clearly satisfy anticipation rejection pursuant to 35 USC 102 (b).

9. The rejection of 35 USC 102 (b) as anticipated by Stamler et al. is maintained.

Applicant argues that the current invention distinguishing from the Stamler et al reference because (1) Stamler et al. teach using ex vivo method not applicable to the recited method and (2) Stamler et al. reference is focused on anemia disease whereas the instant invention is on malaria.

Applicant's arguments have been considered but are not persuasive.

With respect to (1), the recited claim language does not exclude ex vivo treatment. Applicant recites "administering to a *host parasitzed by said Plasmodium species* an agent for a time and under conditions sufficient to inhibit or reduce pathologic adherence properties of the parasitized cells" (See claim 38)(emphasis added). The claim language recites treating "a host parasitized by Plasmodium" which is anticipated by ex vivo treating of Plasmodium infected patients's blood cells (Col. 6, line 5-20; 26-39).

With respect to (2), Stamler et al. also teach using the S-nitrosothiol compounds to treat *infectious disease* other than anemia (Col. 2, line 5-15)(emphasis added).

Therefore, the rejections are deemed proper.

Conclusion

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

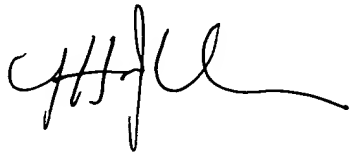
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641



December 30, 2005

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